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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
JEAN-LOUIS, SAMIRA JM	

ART UNIT	PAPER NUMBER
1627	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/531,540	PERC ET AL.	
	Examiner	Art Unit	
	SAMIRA JEAN-LOUIS	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

This Office Action is in response to the amendment submitted on 09/29/09. Claims 34-51 are currently pending in the application, with claims 1-33 having being cancelled. Accordingly, claims 34-51 are being examined on the merits herein.

Receipt of the aforementioned claims is acknowledged and has been entered.

Applicant's argument with respect to the rejection of claims 34-51 over Morris as evidenced by Nakajima has been fully considered. Applicant argues that the instant claims recite the use of an "uncoated" olanzapine while Morris teaches a formulation wherein olanzapine is coated by a polymer. Applicant additionally argues that Morris repeatedly teaches the criticality of coating olanzapine and thus teaches away from uncoated olanzapine. Such arguments are however not persuasive as the Examiner contends that the disclosure of Morris does in fact teach uncoated olanzapine (see Morris, pg. 4, lines 45-48). While Morris exemplifies a coated olanzapine, the Examiner contends that uncoated olanzapine were also taught by Morris since Morris explicitly teaches that uncoated tablets of olanzapine stored at ambient temperature did not show signs of discoloration thereby suggesting that such formulation is indeed within the purview of the skilled artisan. The Examiner reminds applicant that the rejection was rendered obvious and not anticipatory and thus the fact that Morris teaches that uncoated tablets were made and found to be stable for 24 months suggests to one

skilled in the art that such formulation can be made. As for applicant's arguments that Morris teaches away from the used of uncoated tablets, the Examiner maintains that while Morris' invention was directed to a coated olanzapine, Morris also teaches that uncoated olanzapine can be formulated and would remain stable for 24 months unless exposed to air; then such formulations would become discolored by 5 days of air exposure. Thus, the Examiner maintains that in light of Morris who teaches that uncoated tablets can be used without discoloration for up to 5 days (see Morris, pg. 4, lines 45-48), one of ordinary skill in the art would have indeed found it obvious to formulate uncoated tablets of olanzapine if the intended use is for rapid consumption. While applicant argues that such formulation for rapid consumption would be subjected to high manufacturing cost, the Examiner contends that cost of manufacture would not preclude one of ordinary skill in the art to formulate an obvious product taught by the prior art. Moreover, the Examiner contends that a *prima facie* case of obviousness does not hinge on marketing cost but is rather governed by the teaching or suggestion of the prior art and if there is reasonable expectation of success. As for applicant's arguments that olanzapine would become discolored at "any" time, such arguments are not found persuasive as the Examiner maintains that Morris clearly teaches that uncoated olanzapine becomes discolored no later than the 5th day of air exposure, such recitation does not mean that discoloration occurs at any time but rather that by 5 days, discoloration would be noticeable. However, the Examiner maintains that rapid consumption of olanzapine packaged individually when consumed right after opening

would not show any discoloration as taught by Morris. Thus, in view of such teachings the Examiner maintains that Morris does indeed render obvious applicant's invention.

As for applicant's arguments of hindsight reconstruction, the Examiner maintains that because Morris teaches uncoated olanzapine along with pharmaceutical excipients, the Examiner maintains that no discoloration would occur since Morris explicitly teaches that such formulations can in fact be formulated and that no discoloration occurs for 24 months. As a result, the Examiner contends that there is no impermissible hindsight as the suggestion to formulate such tablets came from the teachings of the prior art. Thus, the Examiner maintains that in light of the teachings of Morris, applicant's invention is indeed rendered obvious.

Applicant's contention that Chakrabarty in view of Rubinstein does not render obvious applicant's invention has been fully considered. Applicant argues that Chakrabarty does not teach a homogeneous mixture of uncoated olanzapine and that his method of granulating does not lead to a homogeneous mixture of olanzapine given that not all of the excipients and the active ingredients are dissolved in the granulation liquid. Such arguments are however not found persuasive as Chakrabarty teaches that conventional techniques can be used to make olanzapine formulations. While Chakrabarty does not explicitly teach a homogenous preparation, Chakrabarty does teach formulations of olanzapine tablets made according to conventional techniques and the use of the same excipients as the instant invention. As a result, the Examiner contends that because Chakrabarty teaches the same components as applicant and

teaches the use of conventional techniques to formulate the olanzapine formulations, the instant invention is therefore rendered obvious. While applicant continues to argue that the formulation of Chakrabarty is non-homogeneous, nowhere in Chakrabarty was it disclosed that the composition is non-homogenous and applicant failed to point out exactly where in Chakrabarty was such recitation disclosed. As a result, the Examiner maintains that absent of evidentiary support to demonstrate otherwise, Chakrabarty does in fact teach a homogeneous formulation. Rubinstein, on the other hand, was provided to demonstrate that addition of particular excipients to tablet formulations is well within the skilled of the artisan depending on the properties desired in the tablet formulations. Consequently, the Examiner maintains that Chakrabarty in view of Rubinstein did indeed render obvious applicant's invention.

For the foregoing reasons, the rejections of record under 103 (a) remain proper and are maintained. They are re-stated below for applicant's convenience and being made Final.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 34-51 is rejected under 35 U.S.C. 103 (a) as being unpatentable over Morris et al. (EP 0 830 858 A1, previously cited) as evidenced by Nakajima et al. (U.S. 3,926,817, previously cited).

Morris et al. teach an oral formulation where the active ingredient olanzapine is subcoated and mixed with acceptable excipients (instant claim 34, see abstract and pg. 2, lines 49). The anhydrous form of olanzapine (see pg. 2, lines 54-55) was found to overcome the undesirable discoloration problems of the prior art and found to be stable due to the subcoating of the active ingredient (see pg. 2, lines 35-37 and line 50). The formulation is preferably in an uncoated tablet form (instant claim 32; pg. 8, example 3). Morris et al. further teach that the oral formulation can contain diluents such as lactose, binders such as crospovidone and microcrystalline cellulose, disintegrants such as crospovidone, and lubricants and glidants such as magnesium stearate (instant claims 42-45). Morris et al. further teach that the subcoated form II of olanzapine was used (instant claims 48; see pg. 7, Preparation 2, Form II, lines 15-23) and mixed with 232.12 mg lactose (i.e. 71.4% of b component or oligosaccharide), 13 mg (i.e. 4%) hydroxypropyl cellulose and 40 mg (i.e. 12.3% binder/disintegrant) microcrystalline cellulose (i.e. a total of 16.3% polysaccharide or component (c) or binders), 16.25 mg of crospovidone (i.e. 5% binder) and 1.63 mg of magnesium stearate (i.e. 0.5% lubricant and glidant) (see instant claims 36-41; see pg. 8, example 3). Importantly, Morris et al. teach that the coated olanzapine is blended (i.e. homogeneously mixed) along with the

aforementioned excipients and subsequently compressed with the appropriate tooling on tablet compression equipment (See pg. 8, lines 35-39). Morris et al. do not teach the inclusion of solvent during compression so this meets the limitation of claim 35 of the absence of solvents.

Morris et al. however do not teach the use of an uncoated olanzapine in the oral formulation. Similarly, Morris et al. do not specifically teach a cellulose content of 20-30 weight %, 8-12 weight % of crospovidone, or magnesium stearate in an amount of 0.2-0.4 weight %.

While Morris et al. teach the use of coated olanzapine in the blended mixture, Morris et al. also teach that uncoated olanzapine stored in polyethylene bottles do not show discoloration until exposed to air thus suggesting that non-coated olanzapine can be envisioned in oral formulations. Moreover, Morris et al. further teach that uncoated tablets stored at ambient conditions in amber, high density polyethylene bottles do not show signs of discoloration after 24 months unless the tablets are exposed to open air then discoloration occurs within 5 days (see pg. 4, lines 45-48). Thus, the Examiner contends that it would be within the skilled artisan to formulate the tablets as uncoated tablets if the intended use is for rapid usage of the formulation before the discoloration period and/or for rapid dissolution.

While the exact percentage of the ingredients are not disclosed by Morris, it is generally noted that differences in concentration do not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or dosage is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Given that applicant did not point out the criticality of specific percentages of the invention, it is concluded that the normal desire of scientists or artisans to improve upon what is already generally known would provide the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.

Nakajima et al., on the other hand, have been provided to demonstrate that magnesium stearate is known in the art to be a glidant as well (see col. 8, claim 7).

With regard to Claim 50, the Examiner contends that the ingredients taught by Morris would necessarily form a matrix due to the nature and combination of the excipients. If however, applicant that such matrix is not formed, it is incumbent upon applicant to demonstrate through comparative results that such matrix is not formed as a result of the combination of ingredients taught by Morris. As for claim 51, since the Examiner suggests the use of uncoated tablets and Morris teaches a blended mixture which results in an uncoated tablet, the examiner again contends that the tablet does not form a layered structure.

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize the uncoated olanzapine in the composition of Morris if the desire is for rapid usage before the discoloration time period ensues. Thus, in view of the teachings of Morris et al., one of ordinary skill would have been motivated to utilize uncoated olanzapine in the oral formulation of Morris et al. with the reasonable expectation of providing an oral formulation of olanzapine that rapidly disintegrate and available for fast usage.

Claims 34-51 is rejected under 35 U.S.C. 103 (a) as being unpatentable over Chakrabarti et al. (U.S. 5,229,382,previously cited) in view of Rubinstein et al. (Pharmaceutics: The Science of Dosage Form Design, 1988, Tablets, Chapter 18, pgs. 304-321, previously cited).

Chakrabarti et al. teach the use of olanzapine of formula I in the treatment of disorders of the central nervous system and that the compound has antagonistic properties against the D-1 and D-2 dopamine receptors (see abstract and see col. 2, lines 38-51). Chakrabarti et al. further teach a pharmaceutical composition comprising as active ingredient a compound of formula I or a pharmaceutically acceptable acid addition salt thereof, associated with a pharmaceutically acceptable carrier (see col. 8, lines 16-20). In making the compositions of the invention conventional techniques for the preparation of pharmaceutical compositions may be used wherein the formulation is made in the form of a tablet (see col. 8, lines 20-22 and lines 40-41). Particularly,

Chakrabarti et al. teach the active ingredient of formula I is mixed with a carrier which can be a diluent or excipient (see col. 8, lines 22-29). Suitable carriers include lactose, methyl cellulose, starches, talc, and magnesium stearate (see col. 8, lines 26-35). Chakrabarti et al. additionally exemplify the uncoated olanzapine tablet formulation without any solvent in example 4 where the tablet is made by mixing appropriate diluents such as starches at 68%, lubricants and glidants such as magnesium stearate at 0.3%, disintegrants such as microcrystalline cellulose at 25%, and binders such as povidone at 5.0%, and wherein the tablet is then compressed (instant claims 35, 39-41, 44-45, and 48-49; see col. 11, lines 26-39).

Chakrabarti et al., however, do not teach the use of a monosaccharide as the diluent or the use of 70-80% lactose as the diluent in the oral formulation. Similarly, Chakrabarti et al. do not specifically teach a 3-10 weight % of a binder, 8-12 weight % of povidone, or 3-10 weight % of a disintegrant in the formulation.

Rubinstein et al. teach that a tablet just does not contain the active ingredient (i.e. olanzapine) but also includes other substances known as excipients which have specific functions (see pg. 309, right col., paragraph 2). Particularly, Rubinstein et al. teach the monosaccharide, lactose, as the principal diluent used in the art for bulking the tablet (see pg. 309, right col., paragraph 3). Additionally, Rubinstein et al. teach starches as well-known binding agents and diluents for bulking and as adhesives (see pg. 310, right col., paragraphs 3 and last paragraph; and left col., paragraph 1).

Additionally, Rubinstein teaches the use of glidants in tablets to improve flow properties (see pg. 311, left col., last paragraph). Rubinstein et al. particularly teach that the most commonly used and effective glidant is silica at a concentration of 0.1-0.5 % (see pg. 311, left col., last paragraph).

While Chakrabarti does not specifically teach the exact percentages of the ingredients, it is well within the purview of the skill of the artisan at the time of the invention to adjust the concentration and percentage of the ingredients in the composition during the course of routine experimentation so as to obtain the desirable type of product.

While the exact percentage of the ingredients are not disclosed by Chakrabarti, it is generally noted that differences in concentration do not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Given that applicant did not point out the criticality of specific percentages of the invention, it is concluded that the normal desire of scientists or artisans to improve upon what is already generally known would provide the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.

With regard to Claim 50, the Examiner contends that the ingredients taught by Chakrabarti would necessarily form a matrix due to the nature and combination of the excipients. If however, applicant that such matrix is not formed, it is incumbent upon applicant to demonstrate through comparative results that such matrix is not formed as a result of the combination of ingredients taught by Chakrabarti. As for claim 51, since Chakrabarti does not teach coated olanzapine and Chakrabarti teaches a blended mixture which results in an uncoated tablet, the examiner again contends that the tablet does not form a layered structure.

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize the uncoated olanzapine in the composition of Chakrabarti along with the carriers taught by Chakrabarti in combination since Rubenstein teaches these carriers as well-known excipients in tablet formulations. Thus, in view of the teachings of Chakrabarti et al. and Rubenstein et al., one of ordinary skill would have been motivated to utilize uncoated olanzapine along with carriers taught by Chakrabarti in combination in the oral formulation with the reasonable expectation of providing an oral formulation of olanzapine that is effective in the treatment of central nervous system disorders.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samira Jean-Louis whose telephone number is 571-270-3503. The examiner can normally be reached on 7:30-6 PM EST M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. J. L. /

Examiner, Art Unit 1627

01/17/2010

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627